

REMARKS

Reconsideration and withdrawal of the rejections set forth in the Office action mailed October 11, 2006 are respectfully requested in view of the amendments and arguments presented herein. This Amendment is accompanied by a request for a two month extension of time; this Amendment is thus timely filed.

I. Status of the Claims

Claims 1-107 and 109-188 are pending in the application.

Claims 1-104 and 109-130 are withdrawn from consideration.

Claim 105 is currently amended.

Claim 107 is as originally-presented.

Claims 106, and 131-188 are as previously presented.

Claim 108 is canceled.

The Examiner has indicated that claims 106, 107, and 132-188 are allowable.

II. Amendments to the Claims

Claim 105 has been amended to reflect the feature of a conjugate formed by reaction of an active agent comprising a reactive thiol group with a water-soluble polymer having the structure recited therein. Support for this amendment is found in the language of claim 105 per se.

No new matter has been added to the claims by virtue of the amendments presented herein.

III. Rejections Under 35 U.S.C. §102

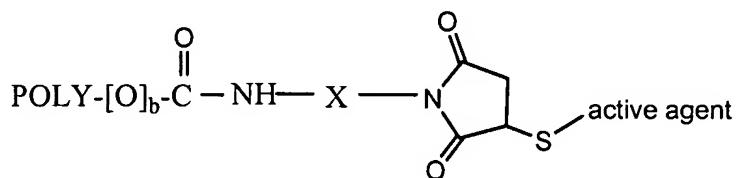
The Examiner has rejected claims 105, 108, and 131 under 35 U.S.C. §102(b) as unpatentable over Yamasaki (WO 2001/48052). A discussion of Yamasaki both herein and in the outstanding Office Action is based on its English language disclosure, US 2003/0219404. It is the Examiner's position that Structure 9 of Table 1 meets the required polymer structure, and that following the stated method of reaction with a terminal amine of a polypeptide would result in the claimed conjugate.

The Examiner has further rejected claim 105 under 35 U.S.C. §102(b) as anticipated by Juszczak et al., Biochemistry 41 (2002), 376-385).

These rejections are respectfully traversed in view of the amendments to the claims as well as the remarks which follow.

A. THE CLAIMED INVENTION

The invention as embodied in the present claims is directed to conjugates of hydrolytically-stable maleimide-terminated water soluble polymers having a particular structural configuration, formed by reaction with an active agent having a thiol (-SH) group. Generally speaking, the conjugates possess the following structural features:



where

POLY is a water-soluble polymer segment,

b is 0 or 1,

X is a hydrolytically stable linker comprising at least 4 contiguous saturated carbon atoms,

"POLY-[O]_b-C(O)-NH-X-" is absent aromatic groups and ester linkages, and

"-S-active agent" represents an active agent comprising a thiol (-SH) group.

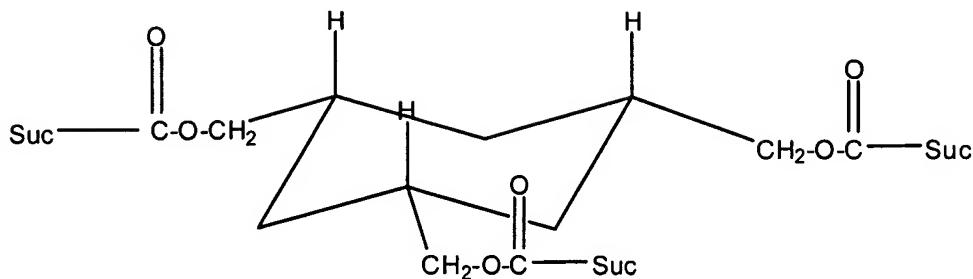
B. THE CITED ART

Yamasaki, M. et al., is directed to branched polyalkylene glycols. In particular, Yamasaki is directed to branched polyalkylene glycols having two single chain polyalkylene glycols linked to a cyclic structure that is non-planar, such as a cycloalkane. The branched polyalkylene glycols are modified with a reactive group

suitable for reaction with an amino acid side chain, N-terminal or C-terminal carboxyl group.

Nowhere does Yamasaki teach a conjugate formed by reaction of a polymer reagent such as those embodied by the Applicant's claims with a thiol-group of a polypeptide or any other active agent. Moreover, a close scrutiny of compound 9 of Table 1 of Yamasaki, relied upon by the Examiner in the instant rejection, reveals a structure that explicitly falls *outside* of the Applicant's claims, due to the presence of 3 rather than 4 contiguous carbon atoms contained within hydrolytically stable linker, X, adjacent to the maleimido nitrogen. Further evidence to this effect is found in Example 9, where the synthesis of Compound 9 is described.

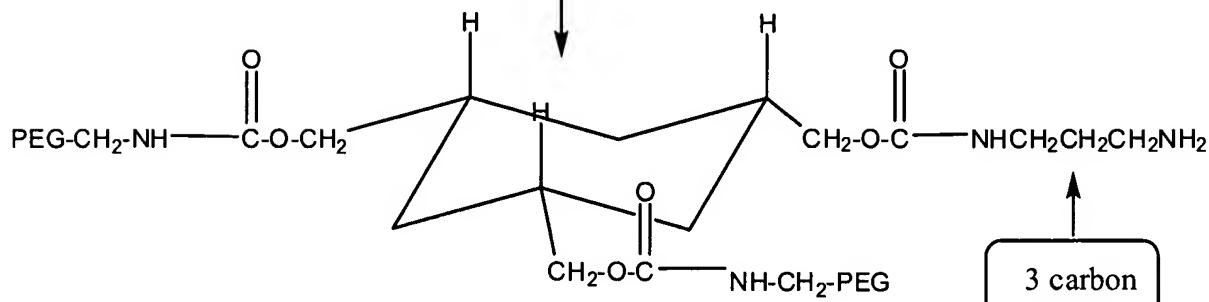
As stated in Example 9, reaction of *cis,cis*-1,3,5-tris(succinimidylcarbonyloxymethyl)cyclohexane with mPEG-NH₂ forms the branched PEG portion of the reagent, followed by reaction with propylene diamine (a **three carbon**-containing diamine) to make a precursor of the final product with only 3 carbon atoms rather than 4. The structures provided below correspond to the synthesis described in Example 9 of Yamasaki. The Examiner will note that although the structure in Table 1, compound 9, possesses two methylenes intervening between the cyclohexane ring and the urethane linkage, the structures below possess only one such methylene, which corresponds to the *actual* compounds prepared based on *cis,cis*-1,3,5-cyclohexane trimethanol as the starting material as described in Example 9. See below.



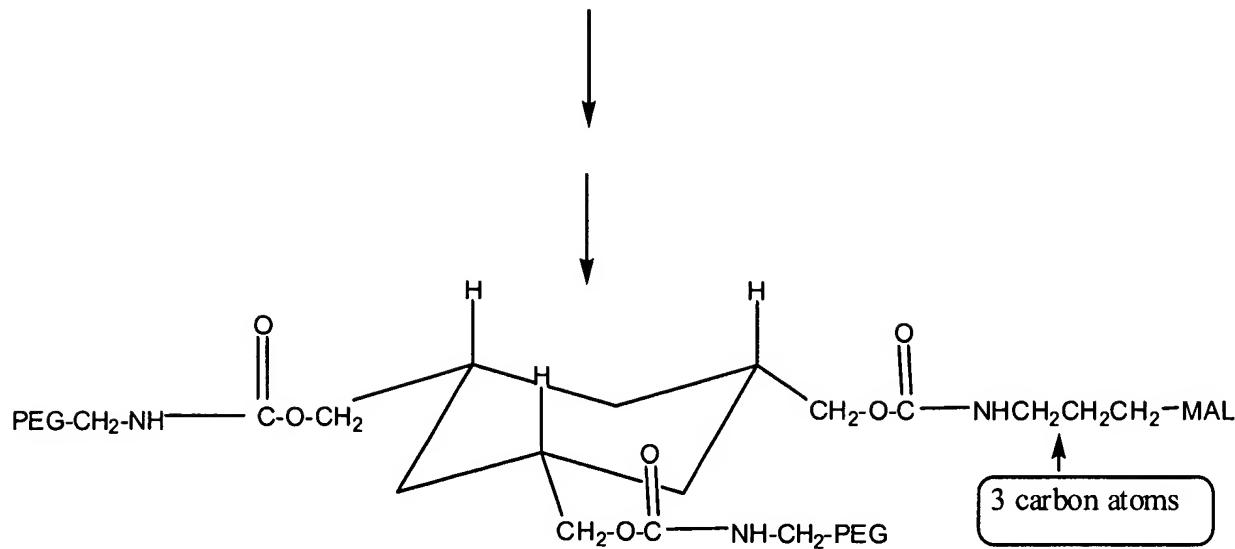
cis,cis-1,3,5-tris(succinimidylcarbonyloxymethyl)cyclohexane

mPEG-NH₂

TEA

NH₂CH₂CH₂CH₂NH₂ (propylene diamine)
3 carbon atoms

Precursor to final product



PRODUCT

Juszczak, L., et al. describes a UV-resonance Raman study to investigate the conformational effects of chemically modifying hemoglobin A modified at the sulphydryl (i.e., thiol) group on Cys β 93 with polyethylene glycol. Eight different maleimide-modified hemoglobins were prepared using various PEG maleimide reagents. None of the PEG reagents employed, and thus, none of their corresponding conjugates, contain four or more contiguous saturated carbon atoms intervening between the maleimide group and \sim NH(CO) \sim , i.e., contained within linker, X, as recited in the Applicant's claims. Moreover, the Applicant's claimed invention explicitly states that "POLY-[O]_b-C(O)-NH-X-" is absent aromatic groups and ester linkages. Both of the structures relied upon the Examiner, structures 3 and 5 on page 377 possess phenyl groups which are indeed aromatic.

C. ANALYSIS

The standard for anticipation is as follows:

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference". *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "Every element of the claimed invention must be literally present, arranged as in

the claim". *Richardson v. Suzuki Motor Co., Ltd*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

In examining the structures taught by each of Yamasaki and Juszczak, for the reasons set out in detail in section B. above, it can be seen that neither reference anticipates the Applicant's claims. First, no where does Yamasaki teach a conjugate formed by reaction with a thiol group of an active agent. Moreover, the maleimide reagent corresponding to compound 9 in Table 1 possesses a 3-saturated carbon linker rather than a linker possessing four or more contiguous saturated carbon atoms as required by the Applicant's claims. Turning now to Juszczak, the maleimide reagents and corresponding conjugates described therein either fail to possess the particular arrangement of atoms specified in the Applicant's claims, or possess an aromatic group – a feature that is explicitly excluded from the polymer-linker portion of the Applicant's claims.

In sum, neither the structures of Yamasaki nor those of Juszczak contain each and every element of the Applicant's claims. Thus, when considered singly, each of Yamasaki and Juszczak fails to anticipate the claimed invention.

In view of the foregoing, it is submitted that the Examiner's rejection of the instant claims under 35 U.S.C. §102(b) should be withdrawn.

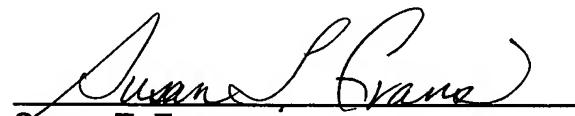
V. CONCLUSION

In view of the foregoing, the Applicant submits that all non-withdrawn claims pending in the application patentably define over the cited art, and are therefore in condition for allowance. The prompt mailing of a Notice of Allowance is therefore earnestly solicited.

If a telephone conference would expedite the prosecution of the subject application, the Examiner is requested to call the undersigned at (650) 838-4406.

Respectfully submitted,

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